



agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des unités de recherche

AERES report on the research unit
Centre National de Génotypage
From the
CEA

May 2010



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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010



Unit

Name of the unit: Centre National de Génotypage

Requested label:

No. in case of renewal:

Unit director: M. Marc LATHROP

Members of the expert committee

Chairperson:

M. Jonathan KNOWLES, EPFL, Lausanne, Switzerland

Reviewers:

M. Olivier DELATTRE, Institut Curie, Paris

M. Wilhelm GRUISSEM, Swiss Federal Institute of Technology, Zürich, Switzerland

M. Hans LEHRACH, Max Plank Institute, Berlin, Germany

M. Michael BOEHNKE, Ann Arbor, USA

Representatives present during the visit

Scientific delegate representing AERES:

M. Nicolas GLAICHENHAUS

Research organisation representative :

Ms. Anne Flürri-HERARD



Report

1 • Introduction

- Date and conduct of the visit:

The visit took place on February 17 and February 18 in Fontenay aux Roses. The unit's director gave a 45 minutes introduction. This was followed by oral presentations by several CNG collaborators as well as by CNG senior staff members.

- History and geographical location of the unit and brief description of its field of study and activities:

The CNG was previously a « Groupement d'Intérêt Public (GIP). It joined the CEA in 2005. It occupies 4500 m² in a building in Evry.

- Management Team:

The head of the unit is M. Marc Lathrop. He is assisted by two deputy directors (M. Ivo Glynne Gut and Ms. Durand), and a direction secretary (Ms. Isabelle Laudier).

The CNG includes :

- A genetic laboratory (Head : M. J. Hager) ;
- A high throughput technology laboratory (Head : M. Gut) ;
- A data analysis and interpretation laboratory (Head : to be recruited) ;
- A translational research laboratory (Head : to be recruited) ;
- A host research laboratory (Head : M. Lathrop) ;



- Staff: (according to the dossier submitted to AERES):

	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	0
N2: Number of EPST, (Public scientific and technological institution) or EPIC, (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	32
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	3
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	42
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	18
N6: Number of doctoral students (see Form 2.8 of the unit's report dossier and 2.7 of the unit's project dossier)	4
N7: Number of persons accredited to supervise research and similar	7



2 • Assessment of the unit

- Overall opinion:

- Very strong world-class leading group essential to keep France in a competitive position in Health Sciences and Crop Sciences ; The CNG is one of the absolutely key elements for the future of French Biology and Medicine and should therefore be funded appropriately in this context going forward.

- The committee members found puzzling that a joint committee was not asked to review both CNG and Genoscope and strongly suggests there should be a joint review organised;

- Strengths and opportunities:

- World-class genotyping and sequencing technologies ;
- Outstanding leader of international reknown ;
- Impressive commitment to data and sample quality, and more specifically a strong bioinformatics expertise ;
- Excellent program and project interface management ;
- Strong collaborative partnership with foreign and French groups ;
- Key participation to large-scale international projects ;
- Synergy between the different projects ;

- Weaknesses and threats:

- ✓ The potential departure of leading scientist(s) is a threat to the the whole of French biomedical research ;
- ✓ In order to remain competitive, significant and additional investment must be made now for the next generation of genomic infrastructure, notably sequencing ;
- ✓ The lack of hiring flexibility even in the european context is a serious handicap in recruiting and maintaining a world-class team ;
- ✓ Increased flexibility for periodically funding of new large-scale instrumentation.

- Recommendations:

- Continue to drive partnerships with clinical groups to create large-scale well phenotype disease-based cohorts for diseases of substantial public health impact ;

- The director should encourage the sequencing team to interact even more closely with other groups ;

- The importance of this structure for France and the international community merits hiring more senior scientists to build and strengthen the key activities in which the CNG participates and particularly with biology groups ;

- In order to remain competitive, the CNG should have access to appropriate funding for collaborative projects outside of the CNG core budget.

3 • Detailed assessments:

- Assessment of work produced and scientific quality:

Since 1999, the CNG has completed 233 projects including 182 national and 51 international. In 2010, 116 projects are ongoing among which:

- 70 are national and 46 international;



- 6 originate from hospitals, 82 from public research institutions, 25 from universities and 3 from the private sector.

Complex trait genomics: The CNG has made a number of important contributions to our understanding of the genomics of complex working in close partnership with French and international groups. The CNGs expertise in running genome-wide association studies is clearly world class and is critical element in the ability of French medical research to play an important role in understanding the molecular pathology of human disease. The diseases studied over the last few years include Alzheimer's Disease, Venous embolism, Asthma, Crohn's disease, Psoriasis, Rheumatoid arthritis and Cardiovascular disease. In all cases the contribution of the CNG has been critical and has allowed significant insights into the molecular causes of these important common diseases.

Programs in cancer genomics: The work at the CNG on cancer genomics has started with a program to identify genes responsible for cancer predisposition, based on whole genome association studies. These analyses have already resulted in the identification of a number of such genes (lung cancer, melanoma, glioma and breast cancer). In a second stage of this program, linked to the ICGC consortium, the CNG has started to identify somatic changes in tumors, based on an analysis of genomic, epigenetic and transcriptome changes by deep sequencing. All programs are first rate, reflecting the strength of the institute in high quality, high throughput, sample handling and sequencing, and informatics.

Single gene disorders: Collections of families and individual cases of dermatological, neurological and metabolic diseases have been gathered. These collections are used for positional cloning strategies and for comprehensive analysis of genotype/phenotype correlations. Some functional and biochemical investigations have been initiated for genes involved in autosomal recessive forms of ichthyosis. Importantly, the group has identified over past years 6 genes that are involved in recessive forms of ichthyosis. Another important project focuses on cutis laxa. The group is involved in an european consortium which is aimed at deciphering the extensive genetic heterogeneity of this disease for which only 30% of the patients present mutations in known predisposing genes. The group has also established in vitro models on reconstituted skin. In addition, the group has identified genes responsible for neutral lipid storage disease with myopathy. Finally, the group has contributed to 2 important publications on the search for genetic modifiers of disease severity in hemoglobinopathies.

Epigenomics projects: Epigenetic mechanisms are increasingly recognised as important components to modifying the genetic regulation mechanisms. The CNG has a very good track record in combining genetic and epigenetic analyses techniques, to generate 'epigenotypes', in different projects (e.g. breast cancer). In addition to these systematic analyses, some additional smaller scale projects address specific epigenetic problems, the role of Tsix as well as the epigenetic regulation of the Prader-Willi syndrome genomic region. Both projects address interesting problems, but could in some cases take much more advantage of the high throughput pipelines available at the CNG to carry out some of the analyses on a genome wide scale.

Applications in other species : In addition to human and mouse, CNG is increasing genotyping efforts in other species, with a particular focus on agronomic crop plants. Rodent models and domestic animals are useful systems because of their well-characterized physiology and various conditions of relevance to human health as well as economic importance in agricultural production. CNG is pursuing a large number of genetic mapping projects with French laboratories and other groups within European projects. CNG is also developing high-density mapping tools for the dog, which develops medical conditions that are particularly relevant to humans. The plant genetics group focuses on association genetics and genetic mapping of QTLs that are useful for breeding to improve crops for increased yield and enhanced resistance to biotic and abiotic stress. Several publications in leading journals have already resulted from the work on crops, which is taking on added urgency as agriculture is facing increasingly unpredictable climatic conditions.

Biological resources (CNG biobank): The CNG biobank contains more than 500 000 biological samples, most of them being DNA samples. The sample handling procedures are standardized with bar coding ensuring a complete sample tracking pipeline. For DNA quality controls, all samples are quantified in terms of DNA concentration and volume determinations and further quality control steps with gel analyses are performed on approximately 10% of samples. To expand the capacity of the CNG biobank new robotic systems are planned in 2010. The samples are handled with excellent QC and sample tracking which ensure optimal conditions for genotyping.

Molecular analysis platforms including platforms for DNA (SNP genotyping, sequencing, microsatellites, DNA methylation (Illumina, Pyrosequencing, Solexa GAI), RNA (Illumina DASL, Affimetrix, qPCR, Solexa GAI), Proteomics (ClinProt, Antibody arrays A2M2S, MS Immuno-histochemistry TAMSIM, LC-MS/MS)



During the period 2006-2009, CNG scientists have 184 peer-reviewed publications. Two-started companies have been created based on patent applications held by the CNG. 11 patents were issued during that period.

Overall, the publications of the CNG are of a very high quality and have a very significant impact internationally. The author list well demonstrates the extensive network of collaborators both in France and internationally that the centre has been able to build over the years. This extensive collaborator network and the publications that the CNG publish each year are a very important to advancing the field of human health. It is also pleasing to note that the CNG also recognises inventions of possible commercial relevance and ensures that these are patented.

- **Assessment of the influence, appeal and integration of the research unit in its environment:**

The Director has a very strong reputation internationally as one of a small number of visionary leaders in the field of the genetics of human disease. Under his leadership the CGN has developed a reputation for world class research, and as importantly he has recruited and developed a number of excellent people that the CNG should endeavour to retain.

In 2008, the CNG budget was 22,600 k€ including 11,500 k€ from the CEA, and 11,100 k€ from external sources including 3,600 k€ from international funding agencies, 75 k€ from ANR, and 7,800 k€ from other national funding agencies.

Beside participating in the EU projects, CNG scientists have obtained 7 ANR grants since 2006.

The CNG is (and has been) involved in a very high number of EU-funded projects including 10 from the FP7 (among which one is coordinated by the CNG), 12 from the FP6, and 10 from the FP5.

- **Assessment of the strategy, governance and life of the unit:**

The CNG has historically focused on ensuring that state of the art equipment is available and applied in the most effective way to the scientific and medical challenges in each of the programs. This has been a critical factor in the very successful track record of the Institute. A number of these platforms are now reaching the end of their lifecycles and it is therefore essential for the CNG to replace these platforms with new even more effective and sensitive systems in order to keep French science at the cutting edge in this key area for Biology and Medicine.

Starting in 2011, the CNG will organize an annual course to teach participants how to manipulate large data sets.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
Non noté	Non noté	Non noté	Non noté	Non noté

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énergie atomique • énergies alternatives

Observations du Centre National de Génotypage (CNG) du CEA

Evry, le 6 septembre 2010

Le CNG remercie l'AERES et le Comité de visite pour l'appréciation globale très positive qu'ils portent sur le développement stratégique et les activités du CNG dans le paysage de la recherche française et européenne.

En tant que Centre national, le CNG note avec satisfaction que le rapport de l'AERES souligne son rôle de leader indispensable pour maintenir, en France, une recherche compétitive sur le plan international en Sciences de la Vie et de la Santé, et en Agronomie, et mentionne son implication dans le développement de partenariats solides avec des groupes de recherche français et européens. Le développement de ce secteur stratégique en France nécessite cependant l'organisation et le financement de grands programmes bien structurés aux côtés du CNG.

Le CNG souhaite compléter la vision d'ensemble qui ressort du rapport de l'AERES en mentionnant aussi que l'intégration du CNG au CEA est un facteur-clé pour faire émerger de ses travaux la filière de la « médecine personnalisée », en développant des applications biomédicales en association avec l'industrie dans un environnement technologique multidisciplinaire unique.

Le CNG a bien noté le besoin indispensable de rester à la pointe des technologies par des investissements substantiels permettant le renouvellement de ses plateformes technologiques de génotypage et de séquençage à grande échelle. Le CNG envisage ce renouvellement à travers des financements pouvant venir du Grand Emprunt pour équiper ses plateformes des dernières technologies, et accroître ainsi son offre de collaborations à la communauté scientifique.

Le CNG met également en oeuvre une stratégie de développement informatique pour gérer des données génomiques massives pouvant atteindre rapidement le pentaflap. Afin d'avoir la puissance de calcul nécessaire, le CNG s'est rapproché du centre de calcul intensif du CEA pour établir une collaboration spécifique au développement de ses activités. Cette collaboration peut aboutir à l'émergence d'un noeud informatique européen dédié à l'étude des maladies et donnerait une grande visibilité en France à ce secteur hautement concurrentiel.

Le CNG considère que l'évaluation séparée du CNG et du Génoscope réalisée par l'AERES est indispensable pour tenir compte des enjeux et des développements spécifiques propres à chaque entité et doit être maintenue à l'avenir.

Pour conclure, le CNG portera toute son attention à l'ensemble des analyses et des recommandations du rapport de l'AERES dont il remercie à nouveau le Comité de visite.

Mark LATHROP

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